inhibitor herbicides (Synchrony™, "STS"). Declaration at ¶5. As described, the RR/LL/STS plant was made by first crossing the A2704 line derived through conventional breeding methodology to contain an ALS resistance gene by backcrossing to stack glyphosate resistance with the STS trait. A glufosinate resistance transgene was then directly transformed into a plant of A2704 creating a STS/LL resistant genotype. Subsequently, A2704STS/RR was crossed to A2704 STS/LL to derive A2704 STS/RR/LL genotypes. *Id.*

Herbicide testing was carried out on the different plants created to determine the degree of herbicide tolerance of these plants. Measurements were made based on percent yield relative to non-herbicide treated control plants following otherwise lethal treatments with the respective herbicides. The results demonstrated that the plants created in Example 13 of the specification were tolerant to glyphosate, glufosinate and ALS inhibitor herbicides. Declaration at ¶6. The results further show that even under the application of all three herbicides, the RR/LL/STS plants maintained no yield loss relative to the control. These results therefore demonstrate full possession of the invention in the working examples.

In view of the foregoing, compliance with the written description requirement has been fully demonstrated. Removal of the rejection is thus respectfully requested.

C Rejection Under 35 U.S.C. §112, First Paragraph – Enablement

The Action rejects claims 1-10 and 13 as lacking enablement under 35 U.S.C. §112, first paragraph, because the specification allegedly does not provide enablement for methods of stacking more than two herbicide resistance genes or the stacking of genes resistant specifically to glyphosate and glufosinate. Applicants respectfully traverse as set forth below.

(1) The Steffen Declaration Establishes Enablement

The enablement of the claims is fully established by the working examples. As explained in the attached Declaration of Donald E. Steffen, working Example 13 of the application, in paragraphs 88-89, describes the creation of a soybean plant comprising genes conferring resistance to glyphosate (Roundup™, "RR"), glufosinate (Liberty Link™, "LL") and ALS inhibitor herbicides (Synchrony™, "STS"). Declaration at ¶5. The RR/LL/STS plant was made by first crossing the A2704 line derived through conventional breeding methodology to contain an ALS resistance gene by backcrossing to stack glyphosate resistance with the STS trait. See Specification at ¶88-89. A glufosinate resistance transgene was then directly transformed into a plant of A2704 creating a STS/LL resistant genotype. Subsequently, A2704STS/RR was crossed to A2704 STS/LL to derive A2704 STS/RR/LL genotypes. *Id.*

Herbicide testing was carried out on the different plants created to determine the degree of herbicide tolerance of these plants. Measurements were made based on percent yield relative to non-herbicide treated control plants following otherwise lethal treatments with the respective herbicides. The results demonstrated that the plants created in Example 13 of the specification are tolerant to glyphosate, glufosinate and ALS inhibitor herbicides. Declaration at ¶6. The results further show that even under the application of all three herbicides the RR/LL/STS plants maintained no yield loss relative to the control. Based on this Mr. Steffen explained that:

> The foregoing further demonstrates that a person of ordinary skill in plant breeding and plant genetics could readily make and use soybean plants and seeds comprising genes conferring resistance to the herbicides glyphosate and glufosinate and a third herbicide tolerance gene using only routine experimentation by following the procedures in the working examples of the application. The results of the herbicide treatment studies further show that such a plant would express the herbicide tolerance genes and exhibit resistance to the respective herbicides.

The Declaration and studies presented in the application therefore more than adequately demonstrate enablement of the full scope of the claims with any soybean plant. The transgenes contained in the seed deposits referenced in the specification may be transferred to any second soybean by the plant breeding techniques described in the working examples using only routine experimentation following the identical techniques described in these examples.

(2) The Claims Under Consideration Do Not Require Stacking More Than Two Resistance Genes

The Action further asserts that the claims are enabled only for two herbicide resistance genes and not for three herbicide resistance genes. In response, it is first noted as explained above that the working examples specifically describe the creation of soybean plants comprising genes conferring resistance to three herbicides and thus enable this subject matter. However, claim 1 only requires genes conferring resistance to glyphosate and glufosinate. The claims requiring three herbicide resistance genes were withdrawn by the Examiner as directed to non-elected subject matter and thus the comments in this regard are moot as not under consideration. Withdrawal of the rejection is thus respectfully requested.

(3) The Specification Provides All Required Materials

As stated above, Applicants have described transgenes providing resistance to glyphosate and glufosinate in the specification by way of deposits of the Asgrow Seed Company proprietary soybean cultivar 924181339 and of the Asgrow Seed Company proprietary soybean cultivar 89248009206 with the ATCC. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1330 (Fed. Cir. 2002). This description alone fully enables the subject matter in connection with any second variety. Example 1, on pp. 19-21 of the specification, describes methods for the introduction of a herbicide resistance gene into any recipient plant and methods for selecting the

transformed tissue as well as regenerating the transformed tissue into whole plants. Example 1 also specifically describes the combination of genes conferring a level of resistance to glyphosate and glufosinate on pp. 21-22. Finally, Examples 8-10 (pp. 53-56) and Example 12 (pp. 57-59) demonstrate the feasibility of combining resistance genes to produce a plant having resistance to at least two herbicides. Because Applicants have (1) described genes which confer resistance to glyphosate and glufosinate, (2) disclosed methods for combining these two genes in one plant, and (3) demonstrated that the combination of two herbicide resistance genes can produce a plant resistant to at least two herbicides, Applicants have enabled the pending claims.

Finally, it must be noted that genes conferring resistance to glyphosate and glufosinate were known in the art. While as explained in great detail below one of skill in the art would not have known prior to the specification teaching that these genes could be used together for benefit or how to do so, the specification overcomes these shortcomings with actual working examples. Applicants therefore cannot be said to lack enablement for this subject matter. It is well settled that "A patent need not teach, and preferably omits, what is well known in the art." See MPEP 2164.01, *citing In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. See MPEP § 2164.01(b), citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The working examples and teaching in the

specification more than demonstrate compliance with this criteria. Removal of the rejection is thus respectfully requested.

D Rejection Under 35 U.S.C. §103

The Action rejects claims 1, 2, 4-10 and 13 as being obvious. In particular, the Action cites Padgette *et al.* as teaching soybean seeds and plants having resistance to glyphosate herbicide and a method of producing hybrid soybean plants that are resistant to glyphosate herbicide. The Action further cites Songstad *et al.* as teaching soybean plants having resistance to glufosinate herbicide. The Action concludes that it would have been obvious to cross the soybean plant of Padgette *et al.* to the soybean plant of Songstad *et al.* to produce a hybrid plant using the methods of Padgette *et al.* Applicants traverse as set forth below.

The previously submitted Declaration of Dr. Joseph R. Byrum explained in specific detail why one of skill in the art would have been without any reasonable expectation of success in arriving at the invention. Dr. Byrum explained, for example, that a soybean variety had never been developed having more than one herbicide resistance transgene combined in a single soybean plant prior to the current invention. It was further explained that the expression of herbicide resistance transgenes requires manipulation of complex metabolic pathways of plant cells. As soybean plants do not naturally exhibit herbicide tolerance, the results of a given modification are unpredictable. Transgene expression further causes complex pleiotropic effects that can vary depending upon factors such as the location of insertion of the transgene in a genome, the transgene being expressed, the genotype of the host soybean plant, and the regulatory elements and any enhancers used to express the transgene. The expression of enzymes not normally present in a plant also creates a "metabolic drag" reducing energy from the

diversion of resources to the expression of the transgene. Dr. Byrum thus concluded that the absence of pleiotropic or other effects preventing the combination of these traits to arrive at the claimed invention would have been speculation prior to the studies in the application and thus one of skill in the art would have been without any reasonable expectation in arriving at the claimed invention as of the filing date. Byrum Declaration, p.4.

The Action, however, asserted that this Declaration was nonpersuasive because (1) phosphinothricin acetyltransferase "is not involved in plant metabolism, thus the gene encoding this enzyme cannot interfere with amino acid synthesis in plants," (2) comments regarding unpredictability of transgene expression and that soybean plants do not naturally exhibit herbicide tolerance are unpersuasive because "nontransgenic resistance to the herbicide glyphosate has been observed in soybean plants and many plants have been produced that are resistant to glyphosate or glufosinate herbicides," (3) comments regarding herbicide resistance transgenes creating a "metabolic drag" are not persuasive because "Applicant has not cited any prior art showing that transforming a plant with EPSPS or PAT would create a metabolic drag," and the references cited are drawn to classical breeding and not transgenic plants, and (4) the Wilcox reference shows that it is possible to cross soybean plants "in order to transfer two traits that are each the result of numerous genes into the same plant," and that the claimed plant need not be made by crossing as transformation would suffice.

As an initial matter it is noted that the rejection makes a number of specific factual assertions that have not been supported with any evidence. For example it is stated that phosphinothricin acetyltransferase "is not involved in plant metabolism." It is also stated that "nontransgenic resistance to the herbicide glyphosate has been observed in soybean plants," but again no basis for this conclusion has been provided. Other conclusory statements are made

while disregarding the teaching in the Declaration without citation to any evidence. It is specifically the burden of the Office to provide "substantial evidence" on the record for all rejections and all factual assertions made. Should the current rejection be maintained, Applicants therefore respectfully request that an affidavit be provided pursuant to 37 C.F.R. §1.104 establishing a factual basis for all of the assertions made in maintaining the §103 rejection. *See* 37 CFR 1.104(c)(2); *see also In re Zurko,*258 F.3d at 1386, 59 USPQ2d at 1697 (Fed. Cir. 2001) ("[T]he Board [or examiner] must point to some concrete evidence in the record in support of these findings" to satisfy the substantial evidence test).

With respect to the contentions made, Applicants note that these do not support the maintenance of the rejection. With regard to assertion (1) that phosphinothricin acetyltransferase "is not involved in plant metabolism, thus the gene encoding this enzyme cannot interfere with amino acid synthesis in plants," Applicants respectfully direct the Examiner to Scheme 1 at page 13 of the specification and surrounding text. This shows that the glufosinate herbicide that PAT acts on inhibits the catalyzation of the conversion of glutamate to glutamine during amino acid biosynthesis. In this regard, Applicants note that is was previously inadvertently stated in paragraph 7 of the Byrum Declaration that glufosinate inhibits PAT, whereas it should have said that glufosinate inhibits glutamine synthetase, and that PAT expression prevents the inhibition of this enzyme by glufosinate. PAT expression in a plant contacted with glufosinate therefore prevents the inhibition of this step and allows amino acid biosynthesis to continue. Incomplete expression of PAT would thus result in inhibition of the conversion of glutamate to glutamine during amino acid biosynthesis. The PAT enzyme therefore *is* involved in plant metabolism of glufosinate-exposed plants and amino acid metabolism in particular in herbicide-treated plants, as is the case with EPSPS. While different amino acids and different branches of the metabolic

pathway are involved, the activities of the enzymes that heterologous EPSPS and PAT expression preserve both catalyze amino acid biosynthesis from molecules sharing the biosynthetic precursor PEP. Prior to the invention and absent evidence to the contrary, it could not have been predicted how heterologous expression of mutant forms of enzymes coupled with exposure to herbicides inhibiting these steps in amino acid biosynthesis would affect plant metabolism whether by feedback inhibition or other means, including levels of the PEP precursor, and in particular whether resistance to both glyphosate and glufosinate could be obtained.

With regard to contention (2) asserting that comments regarding unpredictability of transgene expression based on the normal lack of herbicide resistance in soybeans are unpersuasive because "nontransgenic resistance to the herbicide glyphosate has been observed in soybean plants and many plants have been produced that are resistant to glyphosate or glufosinate herbicides," Applicants note that this also does not support the rejection. First, no evidence is cited in support of the contention. Second, it is incorrect. Soybean plants are not normally herbicide tolerant, whether transgenic or not. Even if it is assumed for purposes of this argument that a nontransgenic mutant soybean plant that is resistant to glyphosate has been observed before, which Applicants do not concede, this is no more relevant to the claims than a soybean plant containing a single herbicide resistance transgene. The fact is that soybeans do not normally exhibit tolerance to glyphosate or glufosinate absent some underlying genetic changes, the combination of which is shown by the Byrum Declaration to have been unpredictable to those of skill in the art as of the filing date. The whole point of the Byrum Declaration is that one of skill in the art could not have predicted prior to the invention how two herbicide resistance transgenes conferring glyphosate and glufosinate tolerance would interact. Regardless of

whether individual plants have been observed resistant to one herbicide, the fact remains that one of skill in the art would not have known how these genes would interact as of the filing date, as emphasized by the normal absence of a herbicide resistance trait in soybeans at all.

With regard to assertion (3) dismissing any "metabolic drag" because "Applicant has not cited any prior art showing that transforming a plant with EPSPS or PAT would create a metabolic drag," and assertion that the references cited are drawn to classical breeding and not transgenic plants, Applicants note that these also do not support the rejection. First, it goes without saying that the expression of a heterologous enzyme creates a metabolic drag. As explained in paragraph 50 of the specification, "In the case of lines containing the introduced PAT gene, energy resources must be diverted to produce the new enzyme at levels suitable to confer herbicide tolerance." Absent sufficiently high levels of heterologous PAT enzyme expression, glufosinate resistance would not be observed and the corresponding deleterious efffects of the herbicide would be observed. The enzymatic activity conferring glyphosate herbicide tolerance is also not possible without expression of sufficient to replace the native enzyme activity that is eliminated by herbicide application. Production of such proteins otherwise not normally present necessarily requires an energy expenditure beyond that of a plant not expressing the heterologous enzymes and thus there is no basis to assert that this does not create a metabolic drag. Expressing two heterologous genes would result in at least twice the drag. Further, the enzymes being expressed and herbicides directly impact plant metabolism. Increases in one enzymatic step in amino acid biosynthesis create increased levels of end product which can result in feedback inhibition and, when genes are combined, the unpredictability of the results is multiplied.

Regarding the references cited in the Byrum Declaration as being nonpersuasive for discussing classical breeding studies, this is irrelevant to the principle explained, which is the relative expectations of success to those of skill in the art as of the filing date. The references show that one of skill in the art would understand that even native genes interact in unpredictable and non-additive ways. This therefore clearly illustrates that the assumptions in the Action that those of skill in the art would predict a mere additive combination of genes conferring glyphosate and glufosinate tolerance are unfounded, especially when considering transgenic and herbicide resistance genes.

Finally, the Action asserted that the Wilcox reference shows that it is possible to cross soybean plants "in order to transfer two traits that are each the result of numerous genes into the same plant," and that the claimed plant need not be made by crossing as transformation would suffice. Again, however, this disregards the point of the Declaration, which was that one of skill in the art would not have a reasonable expectation of success in expressing two ***herbicide*** resistance genes conferring glyphosate and glufosinate tolerance in a single plant. That multiple genes could be transferred into a single plant is irrelevant because the Declaration shows that one of skill in the art would have lacked a reasonable expectation that herbicide resistance transgenes could be expressed in a single plant to obtain resistance to both herbicides. As explained in the Declaration of Dr. Byrum, a soybean variety had never been developed having more than one herbicide resistance transgene combined in a single soybean plant prior to the current invention. The references cited further show that, while some genes could be combined, others could not. No basis whatsoever has been provided to conclude that one of skill in the art would have a reasonable expectation of success in expressing the two genes required by the claims. Finally, that transformation could be used to introduce a transgene as well as by breeding is irrelevant

because this would do nothing to remedy the lack of expectation of success that herbicide tolerance could be obtained to glyphosate and glufosinate.

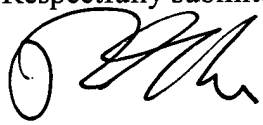
In sum, no basis has been provided for disregarding the evidence presented in the Declaration establishing the non-obviousness of the claims. Findings of fact and conclusions of law by the U.S. Patent and Trademark Office must be made in accordance with the Administrative Procedure Act (APA), 5 U.S.C. § 706(A), (E), 1994. *Dickinson v. Zurko*, 527 U.S. 150, 158 (1999). The APA requires that findings of fact by the Board of Patent Appeals and Interferences must be supported by "substantial evidence" on the record. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). It therefore follows that the Examiner must present "substantial evidence" within the record showing why Dr. Byrum's statements are incorrect. Such evidence, however, has not been provided whereas Applicants have affirmatively presented evidence on the record establishing the non-obviousness of the claims.

In view of the foregoing, removal of the rejection under 35 U.S.C. § 103 is respectfully requested.

E Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. The examiner is invited to contact the undersigned (512)536-3085 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Schillinger *et al.*	Group Art Unit: 1661
Serial No.: 10/052,771	Examiner: Para, A.
Filed: January 23, 2002	Atty. Dkt. No.: ASGR:002USD1
For: PLANTS HAVING RESISTANCE TO MULTIPLE HERBICIDES AND ITS USE	

DECLARATION OF DONALD E. STEFFEN UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Donald E. Steffen, hereby declare that:

1. I have been employed by Monsanto Company ("Monsanto") as a Patent Scientist since 1997, having as my primary responsibility the collection and control of information for the legal protection of Monsanto proprietary varieties.

2. Monsanto is the parent company of wholly owned subsidiary Asgrow Seed Company ("Asgrow"). My duties include the collection and control of information for the legal protection of Asgrow proprietary varieties.

3. I have reviewed and am familiar with the disclosure of U.S. Patent Application Ser. No. 10/052,771 ("the application").

4. I understand that the patent examiner in charge of reviewing the application has asserted that the application does not disclose the creation of a soybean plant comprising genes conferring resistance to the herbicides glyphosate and glufosinate or containing a third herbicide resistance

gene. I understand that the examiner has also asserted that it has not been shown that such a plant would exhibit resistance to both glyphosate and glufosinate or to a third herbicide.

5. I am therefore presenting this declaration to present evidence showing that the application does in fact disclose the creation of a soybean plant containing genes conferring resistance to three herbicides including glyphosate and glufosinate. Specifically, working Example 13 of the application, in paragraphs 88-89, describes the creation of a soybean plant comprising genes conferring resistance to glyphosate (Roundup™, "RR"), glufosinate (Liberty Link™, "LL") and ALS inhibitor herbicides (Synchrony™, "STS"). As described in the application, the RR/LL/STS plant was made by first crossing the A2704 line derived through conventional breeding methodology to contain an ALS resistance gene by backcrossing to stack glyphosate resistance with the STS trait. A glufosinate resistance transgene was then directly transformed into a plant of A2704 creating a STS/LL resistant genotype. Subsequently, A2704STS/RR was crossed to A2704 STS/LL to derive A2704 STS/RR/LL genotypes.

Testing was subsequently carried out by Asgrow Seed Company on the STS/RR/LL and other plants created to determine the degree of herbicide tolerance of these plants. Measurements were made based on percent yield relative to non-herbicide treated control plants following otherwise lethal treatments with the respective herbicides. The tests carried out and results are presented below.

		Application	**Yield***
Variety	**Herbicide**	**Timing**	**(% control)**
A2704	Control	--	100.0
A2704LL	Liberty™ 56 fl oz	V3	100.9
A2704RR	Roundup Ultra™ 32 fl oz	V3	101.5
A2704STS	Synchrony 42DF™ 0.5 oz	V3	98.8
A2704LL/RR/STS	Synchrony 42DF™ 0.5oz/Liberty™ 56 fl oz/Roundup Ultra™ 32	V3	100.3

A2704LL/RR/STS	Synchrony 42DF™ 0.5oz/Liberty™ 56 fl oz/Roundup Ultra™ 32	V3/V3 + 7da	101.0
	LSD(.10)	NS	
	S. E.	8.3	

6. The results demonstrate that the plants created in Example 13 of the specification are tolerant to glyphosate, glufosinate and ALS inhibitor herbicides. The results further show that even under the application of all three herbicides the RR/LL/STS plants maintained no yield loss relative to the control.

7. The foregoing further demonstrates that a person of ordinary skill in plant breeding and plant genetics could readily make and use soybean plants and seeds comprising genes conferring resistance to the herbicides glyphosate and glufosinate and a third herbicide tolerance gene using only routine experimentation by following the procedures in the working examples of the application. The results of the herbicide treatment studies further show that such a plant would express the herbicide tolerance genes and exhibit resistance to the respective herbicides.

8. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 6/23/2005

Donald E. Steffen